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Association of Traumatic Brain Injury With Late-Life Neurodegenerative Conditions and Neuropathologic Findings

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IMPORTANCE The late effects of traumatic brain injury (TBI) are of great interest, but studies characterizing these effects are limited.

OBJECTIVE To determine whether TBI with loss of consciousness (LOC) is associated with an increased risk for clinical and neuropathologic findings of Alzheimer disease (AD), Parkinson disease (PD), and other dementias.

DESIGN, SETTING, AND PARTICIPANTS This study analyzed data from the Religious Orders Study (ROS), Memory and Aging Project (MAP), and Adult Changes in Thought study (ACT). All ROS and MAP participants and a subset of ACT participants consent to autopsy. Studies performed annual (ROS and MAP) or biennial (ACT) cognitive and clinical testing to identify incident cases of dementia and AD. The 7130 participants included members of a Seattle-area health care delivery system (ACT), priests and nuns living in orders across the United States (ROS), and Chicago-area adults in retirement communities (MAP). Of these, 1589 underwent autopsy. Primary hypothesis was that TBI with LOC would be associated with increased risk for AD and neurofibrillary tangles. Data were accrued from 1994 to April 1, 2014.

EXPOSURES Self-reported TBI when the participant was free of dementia, categorized as no more than 1 vs more than 1 hour of LOC.

MAIN OUTCOMES AND MEASURES Clinical outcomes included incident all-cause dementia, AD, and PD in all studies and incident mild cognitive impairment and progression of parkinsonian signs in ROS and MAP. Neuropathologic outcomes included neurofibrillary tangles, neuritic plaques, microinfarcts, cystic infarcts, Lewy bodies, and hippocampal sclerosis in all studies.

RESULTS Of 7130 participants (2879 [40.4%] men; overall mean [SD] age, 79.9 [6.9] years), 865 reported a history of TBI with LOC. In 45 190 person-years of follow-up, 1537 incident cases of dementia and 117 of PD were identified. No association was found between TBI with LOC and incident dementia (ACT: HR for TBI with LOC ≤1 hour, 1.03; 95% CI, 0.83-1.27; HR for TBI with LOC >1 hour, 1.18; 95% CI, 0.77-1.78; ROS and MAP: HR for TBI with LOC ≤1 hour, 0.87; 95% CI, 0.58-1.29; HR for TBI with LOC >1 hour, 0.84; 95% CI, 0.44-1.57) or AD (findings similar to those for dementia). Associations were found for TBI with LOC and incident PD in ACT (HR for TBI with LOC >1 hour, 3.56; 95% CI, 1.52-8.28) and progression of parkinsonian signs in ROS and MAP (odds ratio [OR] for TBI with LOC ≤1 hour, 1.65; 95% CI, 1.23-2.21; OR for TBI with LOC >1 hour, 2.23; 95% CI, 1.16-4.29). Traumatic brain injury with LOC was associated with Lewy bodies (any Lewy body in ACT: RR for TBI with LOC >1 hour, 2.64; 95% CI, 1.40-4.99; Lewy bodies in substantia nigra and/or locus ceruleus in ACT: RR for TBI with LOC >1 hour, 3.30; 95% CI, 1.71-6.38; Lewy bodies in frontal or temporal cortex in ACT: RR for TBI with LOC >1 hour, 5.73; 95% CI, 2.18-15.0; ROS and MAP: RR for TBI with LOC ≤1 hour, 1.64; 95% CI, 1.00-2.70; pooled RR for TBI with LOC ≤1 hour, 1.59; 95% CI, 1.06-2.39) and microinfarcts (any cortical microinfarct in ROS and MAP: RR for TBI with LOC >1 hour, 2.12; 95% CI, 1.12-4.01; pooled RR for TBI with LOC >1 hour, 1.58; 95% CI, 1.06-2.35).

CONCLUSIONS AND RELEVANCE Pooled clinical and neuropathologic data from 3 prospective cohort studies indicate that TBI with LOC is associated with risk for Lewy body accumulation, progression of parkinsonism, and PD, but not dementia, AD, neuritic plaques, or neurofibrillary tangles.

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Author Audio Interview

Supplemental content

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Each year, many people experience a traumatic brain injury (TBI). Most TBIs are mild, and most people return to prior levels of functioning. Worry about late effects of TBI has magnified in recent years with media coverage of chronic traumatic encephalopathy in athletes with repetitive head trauma.[1,2] Head injury is the signature injury of recent military conflicts.[3] Many TBIs are not related to sports or combat. Characterizing the late-life effects of nonrepetitive TBIs in nonathlete civilians is important.[4]

Studies assessing the late effects of TBI have been limited, with few exceptions,[2,5] to outcomes observed during life. Several studies reported associations between TBI with loss of consciousness (LOC) and Alzheimer disease (AD)[6]; the Institute of Medicine[7] concluded that moderate or severe TBI was a risk factor for AD. We sought to determine whether TBI with LOC was associated with late-life dementia, including AD, and Alzheimer-related neuropathologic changes. We hypothesized that TBI with LOC causes accumulation of neurofibrillary tangles and increased risk for AD. We also assessed associations with Parkinson disease (PD), parkinsonism, Lewy bodies, and other neuropathologic changes.

Key Points

Question Is traumatic brain injury (TBI) with loss of consciousness (LOC) associated with late-life clinical evidence of neurodegeneration and neuropathologic findings at autopsy?

Findings In 3 large prospective studies with 7130 participants who were followed for 45 190 person-years and of whom 1589 had comprehensive neuropathologic evaluations at the time of death, TBI with LOC was not associated with the development of mild cognitive impairment, dementia, clinical Alzheimer disease (AD), or Alzheimer pathologic changes. Traumatic brain injury with LOC was associated with the development of Parkinson disease, parkinsonism, Lewy bodies, and microinfarcts.

Meaning Traumatic brain injury with LOC appears to be associated with development of Parkinson spectrum neurodegeneration but not with AD.

Methods

Overview

We evaluated data from the Adult Changes in Thought study (ACT),[8] the Religious Orders Study (ROS),[9] and the Memory and Aging Project (MAP),[10] which are all prospective cohort studies. ROS and MAP were designed to have consistent data acquisition and processing and have been analyzed jointly in numerous reports.[9,10] Rates of TBI exposure in ROS and MAP were similar, and we combined their data. We evaluated associations between TBI and late-life clinical outcomes, including dementia and AD for all 3 studies, mild cognitive impairment (MCI) for ROS and MAP, PD for all 3 studies, and change in parkinsonian signs for ROS and MAP. For those participants in any of the studies who underwent brain autopsy, we evaluated associations between TBI and neuropathologic findings. Studies were approved by the institutional review boards of Group Health Research Institute, University of Washington, and Rush University Medical Center. Participants provided written informed consent. Participants in ROS and MAP signed an Anatomic Gift Act consent donating their brain, and 25% to 30% of ACT participants consented to brain donation.

Parent Studies

ROS started in 1994 and since then has enrolled older religious clergy from more than 40 groups across the United States. MAP started in 1997 and since then has enrolled older residents from Chicago-area retirement facilities and subsidized housing and through church groups and social service agencies. ACT started in 1994 and since then has enrolled older Seattle-area Group Health members. Detailed study design and data collection procedures have been published.[8-12] We analyzed data accrued through April 1, 2014.

TBI Ascertainment

All studies assessed head injuries at enrollment and every study visit, and all captured TBI with LOC; exposure data were collected when participants were known not to have dementia. In ACT, an initial item ascertained whether participants had "an injury so severe that you lost consciousness." If that item was endorsed, subsequent items addressed the type of injury, including head injury, and LOC duration. In ROS and MAP, participants were asked whether they have ever had a head injury, and if so, whether they ever lost consciousness and for how long. We provide further details in eMethods 1 and eTable 1 in the Supplement.

Dementia and AD Ascertainment in ACT

Methods for identifying dementia cases have been published.[8,11,12] Participants were screened every 2 years with the Cognitive Abilities Screening Instrument,[13] a 100-point brief cognitive assessment (lower scores indicate worse cognition). Participants with Cognitive Abilities Screening Instrument scores of less than 86 underwent a standardized diagnostic evaluation, including physical and neurologic examinations and a neuropsychological test battery. Dementia diagnoses were determined at consensus conferences using *DSM-IV* criteria,[14] and AD diagnoses were determined using criteria from the National Institute of Neurological and Communicative Disorders and Stroke.[15] Additional details are provided in eMethods 2 in the Supplement.

MCI, Dementia, and AD Ascertainment in ROS and MAP

Cognitive function in ROS and MAP was assessed annually using a battery of 21 tests, with 19 tests in common.[16] Computer-scored results were reviewed by a neuropsychologist to diagnose cognitive impairment. Participants were then examined by a health care professional who used cognitive and clinical data to identify AD and other dementias.[17] We defined MCI as cognitive impairment in the absence of dementia. Detailed methods have been published[17,18] and are provided in eMethods 2 in the Supplement.

Parkinsonian Features and PD Ascertainment

We used pharmacy data and *International Classification of Diseases, Ninth Revision*, codes from ACT and self-reported data from ROS and MAP to identify PD (eMethods 3 in the Supplement). In ROS and MAP, parkinsonian features are assessed at

every study visit using a modified version of the motor section of the Unified Parkinson's Disease Rating Scale[19] (eMethods 4, eFigure 1, and eTable 2 in the Supplement).

Neuropathologic Protocols

Neuropathologic protocols have been published for ACT[20,21] and ROS and MAP[10,18,22,23]; details are provided in eMethods 5 and eTable 3 in the Supplement. We evaluated neurofibrillary degeneration as measured by Braak stage,[24] neuritic plaque frequency according to the Consortium to Establish a Registry for Alzheimer Disease (CERAD),[25] the presence of cerebral amyloid angiopathy, the presence of macroscopic infarcts, the presence of hippocampal sclerosis, the presence and location of cerebral microinfarcts categorized as deep (basal ganglia or thalamus) vs cortical, and the presence and location of Lewy bodies categorized as present in the substantia nigra or locus ceruleus, the frontal or temporal cortex, or the amygdala. We dichotomized each neuropathologic measure as high vs low or none based on associations with dementia.[21] High measures included Braak stage V or VI, intermediate or frequent CERAD scores, any amyloid angiopathy, any macroscopic infarcts, any microinfarcts, and any Lewy body.

Covariate Ascertainment

Age, sex, and educational level were self-reported. The apolipoprotein E (*APOE*) genotype was obtained from consenting individuals. We adjusted models for *APOE* genotype as presence of 1 or more *APOE* ε4 alleles and tested for interactions with *APOE* genotype and with sex.

Statistical Analysis

We used STATA (version 13.1; StataCorp) for all analyses. We categorized duration of LOC as none vs 1 hour or less vs more than 1 hour. We adjusted models for age at study entry, sex, educational level, and study cohort. Proportional hazards and other model assumptions were tenable for incident PD, so we used Cox proportional hazards regression models for that outcome. We used Weibull models for analyses of dementia, MCI, and AD. We used ordinal mixed-effects models to analyze parkinsonian signs (eMethods 4 in the Supplement provides additional details). We used Poisson regression models for neuropathologic outcomes.

We noted that most of the participants who reported TBI with LOC more than 1 hour were younger than 25 years at the time of their TBI, so we repeated analyses comparing individuals with TBI with LOC at younger than 25 years with people who never reported a TBI with LOC; for these sensitivity analyses we censored people who had a TBI with LOC at 25 years or older.

Authorship Roles

Authorship roles are detailed in eMethods 6 in the Supplement.

Results

A total of 7130 participants had head injury data at enrollment (2879 men [40.4%]; 4251 women [59.6%]; mean [SD] age, 79.9 [6.9] years), including 4265 (59.8%) from ACT and 2865 (40.2%) from ROS and MAP. In ACT, 643 participants (15.1%) reported a TBI with LOC at enrollment; in ROS and MAP, 222 (7.7%) did so. Proportions of people reporting TBI with LOC more than 1 hour were more similar, with 94 from ACT (2.2%) and 48 from ROS and MAP (1.7%). These rates of TBI exposure are intermediate between those reported based on hospital data[26] and those based on extensive injury history questionnaires.[27] Demographic characteristics stratified by history of TBI and duration of LOC are shown in **Table 1** and **Table 2**.[28]

Incident MCI, Dementia, and AD

In ACT, participants with prevalent dementia were not enrolled. One participant was missing educational level data. Of 4264 ACT participants, 3666 (86.0%) had 1 or more follow-up visits. They had a median of 6.2 years of follow-up (interquartile range, 3.9-11.1 years; mean [SD], 7.8 [5.0] years). We identified 921 incident cases of dementia and 759 incident cases of AD in 28 664 person-years of follow-up. We found no statistically significant association between TBI with LOC and dementia risk. Compared with people with no TBI with LOC, people with LOC 1 hour or less had an adjusted hazard ratio (HR) of 1.03 (95% CI, 0.83- 1.27) and those with a TBI with LOC more than 1 hour had an adjusted HR of 1.18 (95% CI, 0.77-1.78).

In ROS and MAP, 2 participants were missing educational level data, and 174 had prevalent dementia. Of 2689 remaining participants, 2452 (91.2%) had at least 1 follow-up visit. They had a median of 4.7 years of follow-up (interquartile range, 2.0-8.0 years; mean [SD], 5.5 [4.1] years). We identified 616 incident dementia cases and 563 incident AD cases in 16 526 person-years of follow-up. We found no statistically significant association between TBI with LOC and dementia risk. The HR for TBI with LOC 1 hour or less was 0.87 (95% CI, 0.58-1.29); for TBI with LOC more than 1 hour, 0.84 (95% CI, 0.44-1.57).

Including *APOE* genotype did not change findings in either study, and we found no significant interactions with *APOE* genotype (eTables 4 and 5 in the Supplement) or sex (eTable 6 in the Supplement). Results for AD were similar to those for dementia (eTables 6-8 in the Supplement). We found no association between TBI with LOC and incident MCI in ROS and MAP (eTable 8 in the Supplement). When we grouped participants by age at TBI exposure, we found no statistically significant association between TBI with LOC and MCI, dementia, or AD (eTables 5, 6, 8, and 9 in the Supplement). When we used the most recent rather than earliest TBI with LOC in ACT, we found few differences (eTable 10 in the Supplement).

Incident PD and Progression of Parkinsonian Signs

We excluded 39 participants with prevalent PD at enrollment in ACT, leaving 3627 with at least 1 follow-up. We identified 83 incident PD cases in 22 800 person-years of follow-up. The adjusted HR for a TBI with LOC 1 hour or less was 0.66 (95% CI, 0.28-1.52); for TBI with LOC more than 1 hour, 3.56 (95% CI, 1.52-8.28).

We excluded 29 participants with prevalent PD at enrollment in ROS and MAP, leaving 2437 with at least 1 follow-up. We identified 34 incident PD cases in 18 156 person-years of

Table 1. Demographic and Functional Characteristics of the ACT Sample Stratified by the Presence vs Absence of TBI and Duration of LOC at Baseline[a]

Variable	No TBI With LOC (n = 3622)	TBI With LOC ≤1 h (n = 470)	TBI With LOC >1 h (n = 94)	TBI With LOC Duration Unknown (n = 79)	Total (n = 4265)
Age at study entry, No. (%)					
65-74 y	2005 (55.4)	290 (61.7)	59 (62.8)	48 (60.8)	2402 (56.3)
75-84 y	1282 (35.4)	150 (31.9)	29 (30.9)	25 (31.6)	1486 (34.8)
≥85 y	335 (9.2)	30 (6.4)	6 (6.4)	6 (7.6)	377 (8.8)
Female sex, No. (%)	2194 (60.6)	196 (41.7)	36 (38.3)	37 (46.8)	2463 (57.7)
Educational level, No. (%)					
≤12 y	1082 (30.0)	115 (24.5)	31 (33.0)	22 (27.8)	1250 (29.3)
13-16 y	1509 (41.7)	191 (40.6)	38 (40.4)	25 (31.6)	1763 (41.3)
≥17 y	1030 (28.4)	164 (34.9)	25 (26.6)	32 (40.5)	1251 (29.3)
Self-reported white race, No. (%)	3288 (90.8)	445 (94.7)	89 (94.7)	76 (96.2)	3898 (91.4)
Functional measure, mean (SD)					
IRT CASI score[b]	0.29 (0.72)	0.39 (0.69)	0.24 (0.66)	0.45 (0.66)	0.31 (0.72)
IADL[c]	0.35 (0.83)	0.36 (0.85)	0.48 (0.95)	0.36 (0.72)	0.35 (0.83)
ADL[d]	0.24 (0.66)	0.22 (0.65)	0.24 (0.61)	0.21 (0.54)	0.24 (0.66)

Abbreviations: ACT, Adult Changes in Thought study; ADL, activities of daily living; IADL, instrumental activities of daily living; IRT CASI, item response theory Cognitive Abilities Screening Instrument score; LOC, loss of consciousness; TBI, traumatic brain injury.

[a] One participant was missing data on educational level; 8, self-reported race; 137, valid IRT CASI scores; 22, IADL; and 20, ADL. Percentages have been rounded and may not total 100.

[b] Scores ranged from −2.69 to 1.75, with higher scores indicating better cognitive functioning.

[c] Scores ranged from 0 to 5, with higher scores indicating greater impairments.

[d] Scores ranged from 0 to 6, with higher scores indicating greater impairments.

Table 2. Demographic and Functional Characteristics of the ROS and MAP Sample Stratified by Presence vs Absence of TBI and Duration of LOC at Baseline

Variable[a]	No TBI With LOC (n = 2643)	TBI With LOC ≤1 h (n = 148)	TBI With LOC >1 h (n = 48)	TBI With LOC Duration Unknown (n = 26)	Total (n = 2865)
Age at study entry, No. (%)					
50-64 y	94 (3.6)	11 (7.4)	1 (2.1)	0	106 (3.7)
65-74 y	792 (30.0)	61 (41.2)	17 (35.4)	13 (50.0)	883 (30.8)
75-84 y	1222 (46.2)	60 (40.5)	22 (45.8)	7 (26.9)	1311 (45.8)
≥85 y	535 (20.2)	16 (10.8)	8 (16.7)	6 (23.1)	565 (19.7)
Female sex, No. (%)	1917 (72.5)	94 (63.5)	31 (64.6)	16 (61.5)	2058 (71.8)
Educational level, No. (%)					
≤12 y	577 (21.8)	32 (21.6)	6 (12.5)	4 (15.4)	619 (21.6)
13-16 y	953 (36.1)	51 (34.5)	17 (35.4)	11 (42.3)	1032 (36.0)
≥17 y	1111 (42.0)	65 (43.2)	25 (52.1)	11 (42.3)	1212 (42.3)
Self-reported white race, No. (%)	2439 (92.3)	139 (93.9)	47 (97.9)	25 (96.2)	2650 (92.5)
Functional measure, mean (SD)					
Global cognitive score[b]	−0.01 (0.65)	0.14 (0.61)	−0.06 (0.78)	−0.03 (0.60)	−0.01 (0.65)
IADL[c]	1.02 (1.58)	0.81 (1.21)	1.23 (1.78)	1.12 (1.51)	1.02 (1.56)
ADL[d]	0.18 (0.67)	0.12 (0.45)	0.21 (0.55)	0.38 (0.80)	0.18 (0.66)
Rosow-Breslau scale score[e]	0.73 (0.97)	0.58 (0.82)	0.79 (0.93)	0.92 (1.02)	0.72 (0.96)

Abbreviations: ADL, activities of daily living; IADL, instrumental activities of daily living; LOC, loss of consciousness; MAP, Memory and Aging Project; ROS, Religious Orders Study; TBI, traumatic brain injury.

[a] Two participants were missing data on educational level; 3, self-reported race; 6, cognition; 12, IADL; 9, ADL; and 12, Rosow-Breslau scale scores. Percentages have been rounded and may not total 100.

[b] Scores ranged from −4.16 to 1.49, with higher scores indicating better cognitive functioning.

[c] Scores ranged from 0 to 8, with higher scores indicating more difficulties with IADLs.

[d] Scores ranged from 0 to 3, with higher scores indicating greater difficulties with ADLs.

[e] Scores ranged from 0 to 3, with higher scores indicating greater impairment.

follow-up. Only 3 individuals with incident PD had reported exposure to TBI with LOC, all of whom had duration of LOC 1 hour or less. Regression results were unstable for TBI with LOC 1 hour or less and undefined for TBI with LOC more than 1 hour.

For evaluation of the progression of parkinsonian signs, we controlled analyses for baseline age, sex, and time since baseline and used the 8-point ordinal variable described in eMethods 3 in the Supplement. The adjusted odds ratio for increasing scores for a history of TBI with LOC 1 hour or less was 1.65 (95% CI, 1.23-2.21); for TBI with LOC more than 1 hour, the odds ratio was 2.23 (95% CI, 1.16-4.29).

Neuropathologic Findings at Autopsy

Of the 4265 ACT participants who had TBI data from study enrollment, autopsy data were available for 525 of 2022 deaths. Of the 2643 ROS and MAP participants who had TBI data at study enrollment, autopsy data were available for 1064 of 1332 deaths. Demographic characteristics were similar to those for the entire cohorts (eTables 11-14 in the Supplement). The frequency of neuropathologic findings is shown in eTables 15 and 16 in the Supplement. Separate regression results for ACT and for ROS and MAP are shown in **Table 3**. We found no association between TBI with LOC 1 hour or less and any neuropatho-

Table 3. Separate Adjusted Associations Between TBI With LOC and Neuropathologic Findings in ACT and in ROS and MAP[a]

	ACT (N = 525)				ROS and MAP (N = 1064)			
	TBI With LOC ≤1 h (n = 80)		TBI With LOC >1 h (n = 14)		TBI With LOC ≤1 h (n = 96)		TBI With LOC >1 h (n = 23)	
Outcome	RR (95% CI)[a]	*P* Value	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value
Braak stage V or VI	1.22 (0.86-1.73)	.26	1.11 (0.61-2.00)	.74	0.87 (0.55-1.37)	.54	0.85 (0.35-2.06)	.71
CERAD intermediate or frequent	1.01 (0.79-1.29)	.92	0.67 (0.36-1.25)	.21	1.01 (0.78-1.31)	.93	1.16 (0.73-1.85)	.54
Amyloid angiopathy	1.08 (0.73-1.59)	.71	1.02 (0.47-2.20)	.96	1.10 (0.88-1.39)	.41	1.11 (0.72-1.71)	.63
Cystic infarcts	0.83 (0.56-1.24)	.37	1.05 (0.52-2.12)	.88	0.95 (0.68-1.33)	.77	1.24 (0.71-2.15)	.45
Hippocampal sclerosis	0.93 (0.41-2.10)	.86	2.34 (1.02-5.30)	.04	0.84 (0.37-1.93)	.68	0.49 (0.07-3.52)	.48
Cerebral microinfarcts								
Any	0.87 (0.64-1.19)	.39	1.23 (0.73-2.09)	.44	1.03 (0.72-1.46)	.88	1.18 (0.63-2.21)	.61
Any cortical	0.92 (0.65-1.31)	.64	1.12 (0.57-2.18)	.74	0.89 (0.53-1.48)	.66	2.12 (1.12-4.01)	.02
Any deep	0.89 (0.60-1.33)	.58	1.67 (0.95-2.93)	.08	1.16 (0.77-1.76)	.48	1.07 (0.47-2.40)	.88
Lewy bodies								
Any	0.93 (0.55-1.59)	.80	2.64 (1.40-4.99)	.003	1.04 (0.67-1.62)	.85	0.95 (0.39-2.31)	.91
Substantia nigra and/or locus ceruleus	0.96 (0.51-1.80)	.89	3.30 (1.71-6.38)	<.001	1.09 (0.69-1.71)	.82	0.82 (0.31-2.22)	.70
Frontal or temporal cortex	1.49 (0.61-3.64)	.38	5.73 (2.18-15.0)	<.001	1.64 (1.00-2.70)	.051	0.74 (0.18-3.00)	.67
Amygdala and/or limbic[c]	1.30 (0.75-2.24)	.35	1.89 (0.69-5.19)	.22	1.16 (0.73-1.84)	.91	0.91 (0.34-2.44)	.85

Abbreviations: ACT, Adult Changes in Thought study; CERAD, Consortium to Establish a Registry for Alzheimer Disease; LOC, loss of consciousness; MAP, Memory and Aging Project; ROS, Religious Orders Study; RR, relative risk; TBI, traumatic brain injury.

[a] Individuals with TBI with LOC of unknown duration were excluded from these analyses.

[b] Models were adjusted for age at death, sex, educational level, and, in the ACT study, study enrollment cohort. The reference category is people with no TBI with LOC.

[c] Lewy bodies were evaluated in the amygdala in the ACT study and in the limbic region in ROS and MAP (see the Methods section and eMethods sections in the Supplement for further details).

Table 4. Adjusted Associations Between TBI With LOC at Any Age and Neuropathologic Findings From Analysis of Pooled Data[a]

	TBI With LOC <1 h (n = 176)		TBI With LOC ≥1 h (n = 37)	
Outcome	RR (95% CI)[b]	*P* Value	RR (95% CI)[b]	*P* Value
Braak stage V or VI	1.02 (0.79-1.33)	.88	0.98 (0.58-1.65)	.93
CERAD criteria intermediate or frequent	1.01 (0.89-1.15)	.88	1.00 (0.79-1.27)	.98
Amyloid angiopathy	1.08 (0.99-1.19)	.09	1.09 (0.93-1.27)	.28
Cystic infarcts	0.90 (0.73-1.12)	.35	1.17 (0.84-1.62)	.34
Hippocampal sclerosis	0.91 (0.51-1.61)	.75	1.34 (0.62-2.89)	.45
Cerebral microinfarcts				
Any	0.94 (0.76-1.15)	.54	1.18 (0.85-1.66)	.32
Any cortical	0.90 (0.68-1.19)	.47	1.58 (1.06-2.35)	.03
Any deep	1.02 (0.78-1.33)	.90	1.30 (0.83-2.05)	.25
Lewy bodies				
Any	1.00 (0.73-1.37)	.99	1.44 (0.87-2.39)	.16
Substantia nigra and/or locus ceruleus	1.04 (0.74-1.45)	.84	1.48 (0.86-2.55)	.16
Frontal or temporal cortex	1.59 (1.06-2.39)	.03	1.75 (0.82-3.77)	.15
Amygdala and/or limbic[c]	1.22 (0.88-1.69)	.24	1.16 (0.59-2.27)	.67

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer Disease; LOC, loss of consciousness; RR, relative risk; TBI, traumatic brain injury.

[a] Across the 3 studies, 1439 people had no reported TBI with LOC.

[b] Adjusted for age at death, sex, educational level, and indicator terms for the Religious Orders Study (ROS) and Memory and Aging Project (MAP) and 3 different enrollment groups for Adult Changes in Thought study (ACT).

[c] Lewy bodies were evaluated in the amygdala in the ACT study and in the limbic region in ROS and MAP (see the Methods section and eMethods sections in the Supplement for further details).

logic finding except Lewy bodies in the frontal or temporal cortex in ROS and MAP (relative risk [RR], 1.64; 95% CI, 1.00-2.70). Participants with TBI with LOC more than 1 hour had an increased risk for cortical cerebral microinfarcts in ROS and MAP (RR, 2.12; 95% CI, 1.12-4.01) and hippocampal sclerosis (RR, 2.34; 95% CI, 1.02-5.30) and Lewy bodies (RR, 2.64; 95% CI, 1.40-4.99) in ACT. We found no interactions with *APOE* genotype (eTable 17 in the Supplement) or sex (eTables 18-20 in the Supplement).

Regression results from pooled analyses are shown in **Table 4**. In pooled analyses, TBI with LOC 1 hour or less was associated with an increased risk for Lewy bodies in the frontal or temporal cortex (RR, 1.59; 95% CI, 1.06-2.39), and TBI with LOC more than 1 hour was associated with an increased risk for cerebral microinfarcts (RR, 1.58; 95% CI, 1.06-2.35) and an even higher point estimate for Lewy bodies in the frontal or temporal cortex, though the 95% CI included the null (RR, 1.78; 95% CI, 0.82-3.77).

Table 5. Adjusted Associations Between TBI With LOC at Younger Than 25 Years and Neuropathologic Findings From Joint Analysis of Data From All 3 Studies[a]

	TBI With LOC <1 h (n = 67)		TBI With LOC ≥1 h (n = 19)	
Outcome[b]	RR (95% CI)[c]	*P* Value	RR (95% CI)[c]	*P* Value
Braak stage V or VI	1.00 (0.66-1.52)	.99	1.03 (0.50-2.14)	.94
CERAD criteria intermediate or frequent	1.09 (0.89-1.32)	.41	0.91 (0.62-1.35)	.65
Amyloid angiopathy	1.07 (0.89-1.29)	.44	0.86 (0.62-1.20)	.38
Cystic infarcts	0.83 (0.58-1.21)	.33	0.84 (0.45-1.60)	.60
Hippocampal sclerosis	1.42 (0.68-2.97)	.35	1.33 (0.37-4.76)	.66
Cerebral microinfarcts				
Any	1.04 (0.78-1.40)	.77	1.66 (1.19-2.32)	.003
Any cortical	1.10 (0.77-1.57)	.60	1.29 (0.71-2.35)	.41
Any deep	1.06 (0.72-1.58)	.76	1.24 (0.64-2.40)	.53
Lewy bodies				
Any	0.95 (0.56-1.62)	.86	1.86 (1.03-3.35)	.04
Substantia nigra or locus ceruleus	1.03 (0.59-1.80)	.91	1.84 (0.94-3.60)	.08
Frontal or temporal cortex	1.53 (0.77-3.03)	.23	2.53 (1.02-6.24)	.045
Amygdala and/or limbic[d]	1.09 (0.60-1.98)	.78	1.77 (0.86-3.64)	.12

Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer Disease; LOC, loss of consciousness; RR, relative risk; TBI, traumatic brain injury.

[a] Across the 3 studies, 1439 people had no reported TBI with LOC.

[b] Only 6 people with TBI with LOC more than 1 h had at least 1 microinfarct, and only 4 people with TBI with LOC more than 1 h had at least 1 Lewy body, so those results may be unstable.

[c] Adjusted for age at death, sex, educational level, and indicator terms for the Religious Orders Study and Memory and Aging Project and 3 different enrollment groups for Adult Changes in Thought study.

[d] Lewy bodies were evaluated in the amygdala in the ACT study and in the limbic region in ROS and MAP (see the Methods section and eMethods sections in the Supplement for further details).

More than one-third of TBI with LOC 1 hour or less and nearly one-half of TBI with LOC more than 1 hour occurred before age 25 years. Among participants with TBI with LOC at younger than 25 years, TBI with LOC more than 1 hour was associated with an increased risk for microinfarcts (RR, 1.66; 95% CI, 1.19-2.32) and Lewy bodies (RR, 1.86; 95% CI, 1.30-3.35), especially in the frontal or temporal cortex (RR, 2.53; 95% CI, 1.02-6.24) (**Table 5**).

Discussion

In 3 prospective cohort studies of older adults free of dementia at baseline and followed up for 45 190 person-years, we did not find associations between TBI with LOC and the risk for incident MCI, AD, or dementia. Of 1537 incident dementia cases across the 3 studies, 1322 were incident AD; we had substantial power for these outcomes. We did not find associations between TBI with LOC and neurofibrillary degeneration or neuritic plaques, although Braak stage V or VI (160 of 525 [30.5%] in ACT and 275 of 1157 [23.8%] in ROS and MAP) and intermediate or frequent neuritic plaques by CERAD criteria (263 of 525 [50.1%] in ACT and 759 of 1157 [65.6%] in ROS and MAP) were common. Including *APOE* genotype had a negligible effect on our results, and we did not find a different risk among *APOE* ε4 carriers. Our total autopsy sample size (1682 autopsies) is nearly 7 times that of a previous evaluation of associations between TBI exposure and Alzheimer pathologic findings[5]; those investigators found associations with neocortical plaques and sex differences that are not confirmed in our study.

Parkinson disease (117 incident cases) and parkinsonian signs are less common than dementia. Despite lower power, we found associations between TBI with LOC both less than 1 hour and more than 1 hour and the progression of parkinsonian signs (in ROS and MAP) and the risk for incident PD (in ACT); no PD cases were found with that exposure in ROS and MAP.

Lewy bodies are less common (89 of 525 [17.0%] in ACT vs 254 of 1157 [22.0%] in ROS and MAP) than neuritic plaques, neurofibrillary tangles, or microinfarcts, but we found associations between TBI with LOC and Lewy body accumulation. Despite lower power, we found associations between TBI with LOC more than 1 hour and Lewy body accumulation in the substantia nigra or the locus ceruleus and in the frontal or temporal cortex in ACT. We found associations between TBI with LOC 1 hour or less and frontal or temporal cortex Lewy bodies in ROS and MAP, and the point estimate was similar for ACT, although the 95% CI in ACT included the null. In pooled analyses, we found associations between TBI with LOC more than 1 hour and cerebral cortical Lewy bodies. A recent study[29] showed an association between TBI in midlife with development of PD a few years later. Some features of synucleinopathies have been identified decades in advance of clinical disease, so the higher rates of TBI with LOC in this group may be the result of, rather than the cause of, PD. We suspect that explanation may be less likely here, because many individuals had exposure 4 or more decades preceding PD. A prior study of TBI exposure and neuropathologic outcomes[5] excluded people with diffuse Lewy bodies from analyses.

Cerebral microinfarcts were common (226 of 525 [43.0%] in ACT and 413 of 1157 [35.7%] in ROS and MAP). Traumatic brain injury with LOC more than 1 hour was associated with an increased risk for cortical microinfarcts in ROS and MAP. The point estimate was elevated in ACT, although the 95% CI

included 1. The pooled analyses showed an association between TBI with LOC more than 1 hour and cerebral cortical microinfarcts. Microinfarcts were identified on hematoxylin-eosin–stained sections; more may have been identified if other stains had been used.

Limitations to this study warrant consideration. The study cohorts may not be broadly representative of the more ethnically diverse US population. As in all cohort studies, unmeasured and residual confounding are always possibilities. Data from the 3 studies were carefully harmonized, autopsies were performed by highly experienced neuropathologists using standard research protocols, and dementia diagnoses were obtained by expert physicians using research quality guidelines; still, systematic differences may be present. Methods for ascertainment of TBI varied across studies and were limited to self-report. Nevertheless, TBI exposure was ascertained at a time when participants were known not to have dementia, and before the development of the incident conditions and neuropathologic evaluations described herein. For PD diagnosis, we were limited to self-report in 2 studies and medications and *International Classification of Diseases, Ninth Revision*, codes in the other. We performed many tests and did not alter our threshold for statistical significance, so it may be prudent to consider our results to be hypothesis generating. Some potentially important confounders were omitted, such as occupational history, smoking, physical activity, body mass index, risk taking, and alcohol intake. There is substantial interest in the effects of repetitive TBI, but the numbers of participants in these studies with more than 1 TBI with LOC were too small to analyze. We did not have data on athletic or military exposures, and the autopsy protocols did not include specific evaluation of chronic traumatic encephalopathy.[30] The ACT autopsy protocol did not specifically include evaluation of diffuse plaques, and none of the protocols was designed specifically for the detection of TBI-related neuropathologic features. The parent studies were designed to study late-onset AD and do not provide information about possible relationships between TBI and early-onset AD. Reverse causation may be a concern in cohort studies with short intervals between exposure and outcome. Reverse causation is less of a concern here, because in sensitivity analyses we limited exposure to participants younger than 25 years. Even in that case, we found an increased risk for Lewy body accumulation and microinfarcts among participants enrolled at older than 65 years and who thus had more than a 40-year lag between exposure and outcome (eFigure 2 in the Supplement).

Conclusions

Several previous studies have suggested associations between TBI with LOC and AD.[6] To our knowledge this study is by far the largest ever on this topic. With more than adequate power to detect an association between TBI with LOC and AD, we found none. We found that TBI with LOC was associated with Lewy body accumulation, progression of parkinsonian features, and the risk for incident PD. These results suggest that a single TBI with LOC is not associated with an increased risk for clinical AD, the accumulation of neuritic plaques, or neurofibrillary degeneration, but rather that the late-life effects of TBI may include Lewy bodies, microinfarcts, PD, and parkinsonism. Traumatic brain injury with LOC sustained early in life is not innocuous and appears to be associated with neurodegenerative conditions, although not AD.

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